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(54) Title: **Alkyl-substituted Pyrazolopyrimidines**

(57) Summary: The invention relates to novel alkyl-substituted pyrazolopyrimidines, methods for the production thereof, and the use thereof for producing drugs to improve cognition, concentration, learning capacity, and/or memory performance.

Description

[0001] The invention relates to novel alkyl-substituted pyrazolopyrimidines, methods for the production thereof, and the use thereof for producing drugs to improve cognition, concentration, learning capacity, and/or memory performance.

[0002] The cellular activation of adenylate or guanylate cyclases effects the cyclization of ATP or GTP to 5'-3' cyclic adenosine monophosphate (cAMP) or 5'-3' cyclic guanosine monophosphate (cGMP). These cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a key role in cellular signal transduction cascades. Both in turn activate, *inter alia* but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A (PKA), and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA or PKG can in turn phosphorylate a variety of cellular effector proteins (e.g., ion channels, G-protein-coupled receptors, structural proteins). In this manner, the second messengers, cAMP and cGMP, can control the most diverse physiological processes in very different organs. The cyclic nucleotides can also act directly on effector molecules, however. Thus, e.g., it is known that cGMP can act directly on ion channels and thereby can influence the cellular ion concentration (overview in: Wei *et al.*, *Prog. Neurobiol.*, **1998**, *56*: 37–64). Phosphodiesterases (PDEs) are a control mechanism to regulate in turn the activity of cAMP and cGMP and thereby these physiological processes. PDEs hydrolyze the cyclic monophosphates to the inactive monophosphates, AMP and GMP. At least 21 PDE genes have been described in the interim (*Exp. Opin. Investig. Drugs*, **2000,** *9*, 1354–3784). These 21 PDE genes can be grouped into 11 PDE families based on their sequence homology (for nomenclature proposals, see http://depts.washington.edu/pde/Nomenclature.html). Individual PDE genes within a family are differentiated with letters (e.g., PDE1A and PDE1B). If further different splice variants occur within a gene, this is then indicated by an additional number after the letter (e.g., PDE1A1).

[0003] Human PDE9A was cloned and sequenced in 1998. The amino acid identity to other PDEs is a maximum of 34% (PDE8A) and a minimum of 28% (PDE5A). With a Michaelis-Menten constant (K_m value) of 170 nM, PDE9A has a high affinity for cGMP. Moreover, PDE9A is selective for cGMP (K_m value for cAMP = 230 μM). PDE9A exhibits no cGMP binding domains, which suggested allosteric enzyme regulation by cGMP. It was demonstrated with a western blot analysis that PDE9A is expressed in humans in testes, brain, small intestine, musculoskeletal system, heart, lung, thymus, and spleen. The highest expression was found in the brain, small intestine, heart, and spleen (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25): 15559–15564). The gene for the human PDE9A is` located on chromosome 21q22.3 and contains 21

exons. Four alternative splice variants of PDE9A have been identified to date (Guipponi *et al.*, *Hum. Genet.*, **1998**, *103*: 386–392). Classic PDE inhibitors do not inhibit human PDE9A. Thus, IBMX, dipyridamole, SKF94120, rolipram, and vinpocetine in concentrations up to 100 μM exhibit no inhibition of the isolated enzyme. An IC_{50} value of 35 μM was determined for zaprinast (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25): 15559–15564).

[0004] Mouse PDE9A was cloned and sequenced in 1998 by Soderling *et al.* (*J. Biol. Chem.*, **1998**, *273* (19): 15553–15558). Like the human form, it has a high affinity for cGMP with a Km of 70 nM. An especially high expression was found in the mouse kidney, brain, lung, and heart. Mouse PDE9A is also not inhibited by IBMX at concentrations below 200 μM; the IC_{50} value for zaprinast is 29 μM (Soderling *et al.*, *J. Biol. Chem.*, **1998**, *273* (19): 15553–15558). It was shown in the rat brain that PDE9A is highly expressed in certain brain regions. These include the olfactory bulb, hippocampus, cortex, basal ganglia, and basal forebrain (Andreeva *et al.*, *J. Neurosci.*, **2001**, *21* (22): 9068–9076). The hippocampus, cortex, and basal forebrain in particular play an important role in learning and memory processes.

[0005] As already mentioned above, PDE9A is distinguished by an especially high affinity for cGMP. For this reason, PDE9A, in contrast to PDE2A (K_m = 10 μM; Martins *et al.*, *J. Biol. Chem.*, **1982**, *257*: 1973–1979), PDE5A (K_m = 4 pM; Francis *et al.*, *J. Biol. Chem.*, **1980**, *255*: 620–626), PDE6A (K_m = 17 μM; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, *263* (17): 8133–8141) and PDE11A (K_m = 0.52 μM; Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, *97* (7): 3702–3707), is already active even at low physiological concentrations. In contrast to PDE2A (Murashima *et al.*, *Biochemistry*, **1990**, *29*: 5285–5292), the catalytic activity of PDE9A is not increased by cGMP, because it has no GAF domains (cGMP binding domains through which the PDE activity is allosterically increased) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, *12*: 174–179). For this reason, PDE9A inhibitors lead to an increase in the basal cGMP concentration. This increase in the basal cGMP concentration surprisingly leads to an improvement in learning capacity and memory performance in the social recognition test.

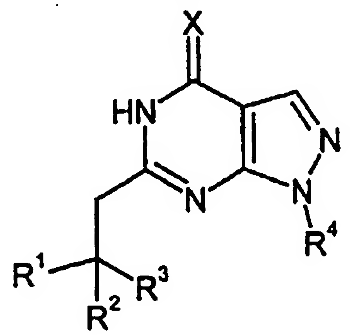
[0006] WO 98/40384 discloses pyrazolopyrimidines, which stand out as PDE1, 2, and 5 inhibitors and can be used for the treatment of cardiovascular and cerebrovascular diseases, as well as urogenital diseases.

[0007] Pyrazolopyrimidines with coronary dilating action are described in CH 396 924, CH 396 925, CH 396 926, CH 396 927, DE 1 147 234, DE 1 149 013, and GB 937,726; these can be used for the treatment of myocardial circulatory disorders.

[0008] Pyrazolopyrimidines, which have an anti-inflammatory and blood sugar-lowering action, are described in US 3,732,225.

[0009] DE 2 408 906 describes styrene pyrazolopyrimidines, which can be used as antimicrobial and anti-inflammatory agents for the treatment of, for example, edema.

[0010] The present invention relates to compounds of the formula



(I),

where

R^1 stands for C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, $-C(=O)OR^5$, or $-C(=O)NR^6R^7$, whereby C_1-C_6 alkyl is optionally substituted with hydroxy, C_1-C_6 alkoxy, $-C(=O)OR^5$, or $-C(=O)NR^6R^7$, and

R^5 for C_1-C_6 alkyl,

R^6 and R^7 independently of one another stand for hydrogen, C_6-C_{10} aryl, C_1-C_6 alkyl, or, together with the nitrogen atom to which they are bound, form a 4- to 10-membered heterocyclyl,

R^2 stands for hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy,

or

R^1 and R^2, together with the carbon atom to which they are bound, form C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, or a 4- to 10-membered heterocyclyl, which are optionally substituted with up to 2 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, oxo, and $-C(=O)OR^8$, and

R^5 stands for C_1-C_6 alkyl or benzyl,

R^3 represents hydrogen or C_1-C_6 alkyl,

R^4 pentan-3-yl or C_4-C_6 cycloalkyl,

X oxygen or sulfur,

and salts thereof, solvates, and/or solvates of the salts.

[0011] The compounds of the invention can exist in stereoisomeric form (enantiomers, diastereomers) depending on their structure. The invention for this reason relates to the enantiomers or diastereomers and the specific mixtures thereof. Stereoisomerically uniform

components can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

[0012] Physiologically compatible salts of the compounds of the invention are preferred as salts within the scope of the invention.

[0013] Physiologically compatible salts of compounds (I) comprise acid addition salts of mineral acids, carboxylic acids, and sulfonic acids, e.g., salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid, and benzoic acid.

[0014] Physiologically acceptable salts of compounds (I) also comprise salts of customary bases, such as, for example and preferably, alkali metal salts (e.g., sodium and potassium salts), alkaline earth salts (e.g., calcium and magnesium salts) and ammonium salts, derived from ammonia or organic amines having 1 to 16 C atoms, such as, for example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, dehydroabietylamine, arginine, lysine, ethylenediamine, and methylpiperidine.

[0015] Designated as solvates within the scope of the invention are the forms of the compounds that in the solid or liquid state form a complex through coordination with solvent molecules. Hydrates are a special form of solvates, in which the coordination occurs with water.

[0016] Within the scope of the present invention, the substituents, if not otherwise specified, have the following meaning:

C_1-C_6 alkoxy stands for a straight-chain or branched alkoxy radical having 1 to 6, preferably 1 to 4, and especially preferably 1 to 3 carbon atoms. Nonlimiting examples comprise methoxy, ethoxy, *n*-propoxy, isopropoxy, *tert*-butoxy, *n*-pentoxy, and *n*-hexoxy.

[0017] C_1-C_6 alkyl stands for a straight-chain or branched alkyl radical having 1 to 6, preferably 1 to 4, and especially preferably 1 to 3 carbon atoms. Nonlimiting examples comprise methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl, *n*-pentyl, and *n*-hexyl.

[0018] C_6-C_{10} aryl stands for phenyl or naphthyl.

[0019] C_3-C_8 cycloalkyl stands for cyclopropyl, cyclopentyl, cyclobutyl, cyclohexyl, cycloheptyl, or cyclooctyl. Cyclopropyl, cyclopentyl and cyclohexyl are preferred.

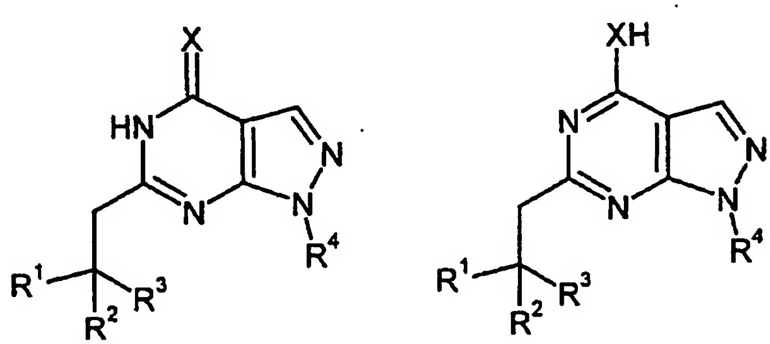
[0020] C_3-C_8 cycloalkenyl stands for partially unsaturated, nonaromatic cycloalkyl radicals, which contain one or a plurality of multiple bonds, preferably double bonds. Nonlimiting examples comprise cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0021] Halogen stands for fluorine, chlorine, bromine, and iodine. Fluorine, chlorine, and bromine are preferred, and fluorine and chlorine especially preferred.

[0022] A 4- to 10-membered heterocyclyl stands for a mono- or polycyclic, heterocyclic radical having 4 to 10 ring atoms and up to 3, preferably 1 heteroatom(s) or hetero group(s) selected from the series consisting of *N*, O, S, SO, and SO_2. A 4- to 8-membered heterocyclyl is preferred. A mono- or bicyclic heterocyclyl is preferred. *N* and O are preferred as heteroatoms. The heterocyclyl radicals can be saturated or partially unsaturated. Saturated heterocyclyl radicals are preferred. The heterocyclyl radicals can be bound via a carbon atom or a heteroatom. Especially preferred are 5- to 7-membered, monocyclic saturated heterocyclyl radicals having up to two heteroatoms selected from the series consisting of O, *N*, and S. The following are named as examples and with preference: oxetan-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, tetrahydrofuranyl, tetrahydrothienyl, pyranyl, piperidinyl, thiopyranyl, morpholinyl, and perhydroazepinyl.

[0023] If radicals in the compounds of the invention are optionally substituted, if not otherwise specified, substitution with up to three identical or different substituents is preferred.

[0024] The compounds of the invention can also be present as tautomers, as is shown by way of example below:



[0025] Another embodiment of the invention relates to compounds of formula (*n*, where

R^1 stands for C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, -C(=O)OR^5, or -C(=O)NR^{6}R^7, whereby C_1-C_4 alkyl is optionally substituted with hydroxy, C_1-C_4 alkoxy, -C(=O)OR^5, or -C(=O)NR^{6}R^7, and

R^5 stands for C_1-C_4 alkyl,

R^6 and R^7 independently of one another for hydrogen, phenyl, and C_1-C_4 alkyl, or, together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclyl,

R^2 stands for hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy,

or

R^1 and R^2, together with the carbon atom to which they are bound, form C_5-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, or a 5- to 6-membered heterocyclyl, which are optionally substituted with up to 2 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, oxo, and -C(=O)OR^8, and

R^8 stands for C_1-C_4 alkyl or benzyl,

R^3 represents hydrogen,

R^4 pentan-3-yl or C_5-C_6 cycloalkyl,

X oxygen or sulfur,

and salts thereof, solvates, and/or solvates of the salts.

[0026] Another embodiment of the invention relates to compounds of formula (I), where

R^1 stands for methyl, ethyl, isopropyl, methoxycarbonyl, ethoxycarbonyl, or -C(=O)NR^6R^7, whereby methyl is optionally substituted with methoxycarbonyl or ethoxycarbonyl, and

R^6 for phenyl, and

R^7 for hydrogen,

R^2 represents hydrogen, methyl, or

R^1 and R^2, together with the carbon atoms to which they are bound, form cyclopentyl, cyclohexyl, cyclopentenyl, or tetrahydrofuryl, whereby cyclohexyl is optionally substituted with methyl, and

R^3 represents hydrogen,

R^4 pentan-3-yl or C_5-C_6 cycloalkyl,

X oxygen or sulfur,

and salts thereof, solvates, and/or solvates of the salts.

[0027] Another embodiment of the invention relates to compounds of formula (I), where

R^1 stands for methyl, ethyl, isopropyl, methoxycarbonyl, ethoxycarbonyl, or -C(=O)NR^6R^7, whereby methyl is optionally substituted with methoxycarbonyl or ethoxycarbonyl, and

R^6 for phenyl, and

R^7 for hydrogen,

R^2 represents hydrogen, methyl, or

R^1 and R^2, together with the carbon atoms to which they are bound, form cyclopentyl, cyclohexyl, cyclopentenyl, or tetrahydrofuryl, whereby cyclohexyl is optionally substituted with methyl, and

R^3 represents hydrogen,

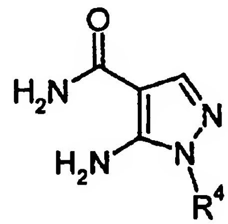
R^4 pentan-3-yl or C_5-C_6 cycloalkyl,

X oxygen,

and salts thereof, solvates, and/or solvates of the salts.

[0028] In addition, a method for the preparation of the compounds of the invention of formula (I) was found, characterized in that either

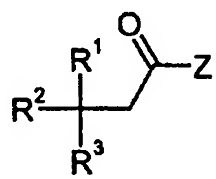
[A] compounds of the formula



(II),

where R^4 has the aforementioned meanings,

are converted by reaction with a compound of the formula



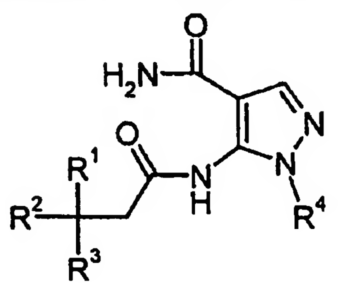
(IIIa),

where R^1, R^2 and R^3 have the aforementioned meanings

and

Z stands for chlorine or bromine,

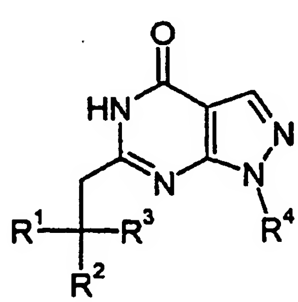
in an inert solvent and in the presence of a base, first into compounds of the formula



(IV),

where R^1, R^2, R^3, and R^4 have the aforementioned meanings,

then cyclized in an inert solvent in the presence of a base, to compounds of the formula

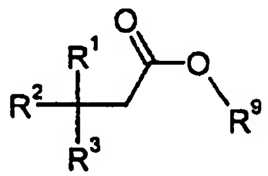


(IA),

where R^1, R^2, R^3, and R^4 have the aforementioned meanings,

or

[B] compounds of formula (II) are reacted with direct cyclization to (IA) with a compound of the formula



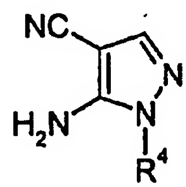
(IIIb),

where R^1, R^2, and R^3 have the aforementioned meanings and

R^9 stands for methyl or ethyl,

in an inert solvent and in presence of a base, or

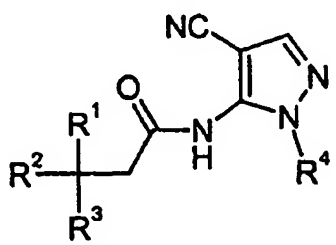
[C] compounds of the formula



(V),

where R^4 has the aforementioned meanings,

are converted first by reaction with a compound of formula (IIIa) in an inert solvent and in the presence of a base, into compounds of the formula

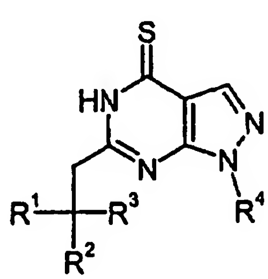


(VI),

where R^1, R^2, R^3, and R^4 have the aforementioned meanings,

and these are cyclized to (IA) in a second step in an inert solvent and in the presence of a base and an oxidizing agent,

and the compounds of formula (IA) are then converted optionally by reaction with a sulfurizing agent, such as, for example, diphosphorus pentasulfide, into the thiono derivatives of the formula



(IB),

where R^1, R^2, R^3, and R^4 have the aforementioned meanings,

and the resulting compounds of formula (I) are optionally reacted with the appropriate (i) solvents and/or (ii) bases or acids to their solvates, salts, and/or solvates of the salts.

[0029] Inert organic solvents that do not change under the reaction conditions are suitable for the first step of process [A] and process [C]. These include preferably ethers such as, for example, diethyl ether, dioxane, tetrahydrofuran, or glycol dimethyl ether, or toluene, or pyridine. It is also possible to use mixtures of the said solvents. Tetrahydrofuran, toluene, or pyridine is especially preferred.

[0030] Suitable bases are in general alkali hydrides such as, for example, sodium hydrides, or cyclic amines such as, for example, piperidine, pyridine, dimethylaminopyridine (DMAP), or C_1-C_4 alkylamines such as, for example, triethylamine. Sodium hydride, pyridine, and/or dimethylaminopyridine are preferred.

[0031] The base is generally used in an amount of 1 mol to 4 mol, preferably 1.2 mol to 3 mol, in each case based on 1 mol of the compounds of general formula (II) or (V).

[0032] In a variant, the reaction is carried out in pyridine to which a catalytic amount of DMAP is added. Optionally toluene can also be added.

[0033] The reaction temperature can be varied in general over a rather broad range. In general, the reaction is run in a range of –20°C to +200°C, preferably 0°C to +100°C.

[0034] The customary organic solvents are suitable as the solvent for the cyclization in the second step of processes [A] and [C]. These include preferably alcohols such as methanol, ethanol, propanol, isopropanol, *n*-butanol, or *tert*-butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide, or dimethylsulfoxide. Alcohols such as methanol, ethanol, propanol, isopropanol, or *tert*-butanol are used with particular preference. It is also possible to use mixtures of the said solvents.

[0035] Customary inorganic bases are suitable as bases for the cyclization in the second step of processes [A] and [C]. These include preferably alkali hydroxides or alkaline earth hydroxides such as, for example, sodium hydroxide, potassium hydroxide, or barium hydroxide, or alkali carbonates such as sodium or potassium carbonate or sodium bicarbonate, or alkali alcoholates, such as sodium methanolate, sodium ethanolate, potassium methanolate, potassium ethanolate, or potassium-tert-butanolate. Especially preferred are potassium carbonate, sodium hydroxide, and potassium-tert-butanolate.

[0036] In carrying out the cyclization, the base is generally used in an amount of 2 mol to 6 mol, preferably 3 mol to 5 mol, in each case based on 1 mol of the compounds of the general formula (IV) or (VI).

[0037] Hydrogen peroxide or sodium borate, for example, is suitable as an oxidizing agent for the cyclization in the second step of process [C]. Hydrogen peroxide is preferred.

[0038] The cyclization in processes [A], [B] and [C] is generally performed within a temperature range of 0°C to +160°C, preferably at the boiling point of the specific solvent.

[0039] The cyclization is generally performed at normal pressure. It is also possible, however, to carry out the process at excess or low pressure (e.g., in a range of 0.5 to 5 bar).

[0040] The alcohols listed above for the second step of processes [A] and [C] are suitable as solvents for process [B], ethanol being preferred.

[0041] Alkali hydrides such as, for example, sodium or potassium hydride, or alkali alcoholates such as, for example, sodium methanolate, ethanolate, isopropylate, or potassium-tert-butylate, are suitable as bases for process [B]. Sodium hydride is preferred.

[0042] The base is used in an amount of 2 mol to 8 mol, preferably 3 mol to 6 mol, in each case based on 1 mol of the compounds of formula (In. [*sic*]

[0043] The compounds of formula (II) are known or, for example, can be prepared by condensing first ethoxymethylene malonic acid dinitrile with hydrazine derivatives of formula (VII)

R^4-NH-NH (VII),

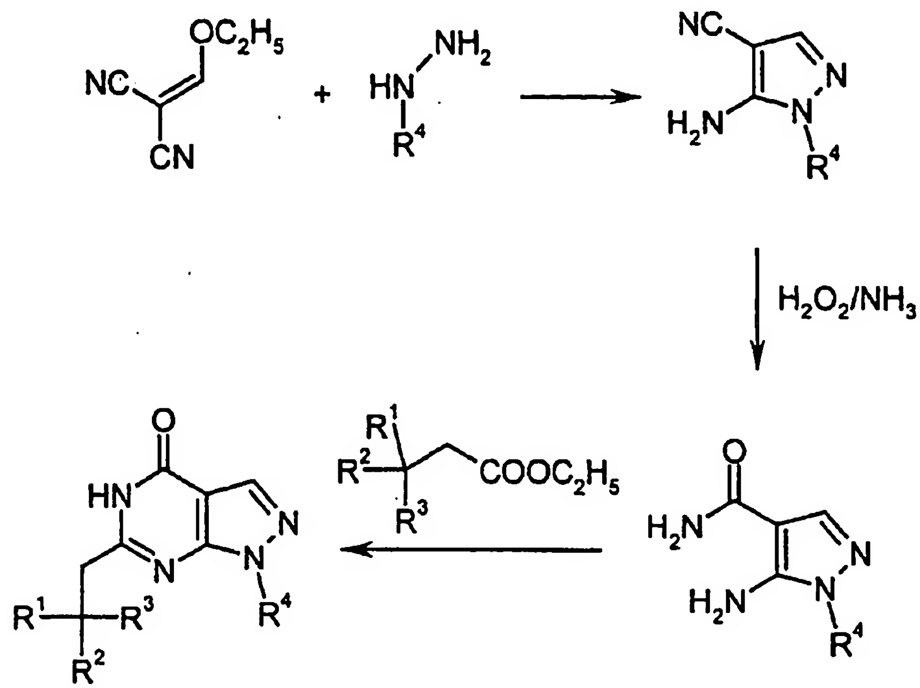
where R^4 has the aforementioned meanings,

in an inert solvent to the pyrazole nitriles of formula (V) and then reacting these compounds with one of the aforementioned oxidizing agents, preferably hydrogen peroxide, in the presence of ammonia [cf., e.g., A. Miyashita *et al.*, *Heterocycles* **1990,** *31*, 1309ff].

[0044] The compounds of formulas (IIIa), (IIIb), and (VII) are obtainable commercially, known from the literature, or can be prepared in analogy to methods known from the literature.

[0045] The process of the invention can be explained by way of example with use of the following formula scheme:

Scheme



[0046] Compounds of formula (IA) and (IB) optionally can be modified further within the range of meaning of R^1, R^2, and R^3 according to standard methods.

[0047] Other methods for the preparation of pyrazolo[3,4-d]pyrimidin-4-ones are known and can also be used for the synthesis of the compounds of the invention (see, for example: P. Schmidt *et al.*, Helvetica Chimica Acta, **1962**, *189*, 1620ff).

[0048] The compounds of the invention showed an unforeseeable, valuable pharmacological action spectrum.

[0049] Surprisingly it was found that selective PDE9A inhibitors are suitable for the preparation of drugs to improve cognition, concentration, learning capacity, or memory performance.

[0050] The compounds of the invention can be used by virtue of their pharmacological properties alone or in combination with other drugs to improve cognition, concentration, learning capacity, and/or memory performance.

[0051] A PDE9A inhibitor within the meaning of the invention is a compound, with an IC_{50} value of less than 10 µM, preferably less than 1 µM, which [inhibits] human PDE9A under the conditions given below.

[0052] A selective PDE9A inhibitor within the meaning of the invention is a compound, which inhibits human PDE9A under the conditions given below more greatly than human PDE1C, PDE2A, PDE3B, PDE4B, PDE5A, PDE7B, PDE8A, PDE10A, and PDE11. A ratio of IC_{50}

(PDE9A)/IC_{50} (PDE1C, PDE2A, PDE3B, PDE4B, PDE5A, PDE7B and PDE10A) is preferably less than 0.2.

[0053] The selective PDE9A inhibitors are especially suitable for improving cognition, concentration, learning capacity, or memory performance after cognitive disorders, as occur especially in situations/illnesses/syndromes such as "mild cognitive impairment," age-related learning and memory disorders, age-related loss of memory, vascular dementia, head injury, stroke, dementia occurring after strokes ("post-stroke dementia"), post-traumatic dementia, general concentration disorders, concentration disorders in children with learning and memory problems, Alzheimer's disease, dementia with Lewy bodies, dementia with frontal lobe degeneration including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob disease, HIV dementia, schizophrenia with dementia, or Korsakoff's psychosis.

[0054] The in vitro action of the compounds of the invention can be demonstrated with the following biological assays:

PDE Inhibition

[0055] Recombinant PDE1C (GenBank/EMBL accession number: NM_005020, Loughney *et al.*, *J. Biol. Chem.*, **1996** *271*, 796-806), PDE2A (GenBank/EMBL accession number: NM_002599, Rosman *et al.*, *Gene*, **1997** *191*, 89-95), PDE3B (GenBank/EMBL accession number: NM_000922, Miki *et al.*, *Genomics*, **1996**, *36*, 476-485), PDE4B (GenBank/EMBL accession number: NM_002600, Obernolte *et al.*, *Gene.*, **1993**, *129*, 239-247), PDE5A (GenBank/EMBL accession number: NM_001083, Loughney *et al.*, *Gene*, **1998**, *216*, 139-147), PDE7B (GenBank/EMBL accession number: NM_018945, Hetman *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, **2000**, *97*, 472-476), PDE8A (GenBank/EMBL accession number: AF_056490, Fisher *et al.*, *Biochem. Biophys. Res. Commun.*, **1998** *246*, 570-577), PDE9A (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25): 15559–15564), E10A [*sic*] (GenBank/EMBL accession number: NM_06661, Fujishige *et al.*, *J. Biol. Chem.*, **1999**, *274*, 18438-45), PDE11A (GenBank/EMBL accession number: NM_016953, Fawcett *et al.*, *Proc. Natl. Acad. Sci.*, **2000**, *97*, 3702-3707) were expressed using the pFASTBAC Baculovirus Expression System (GibcoBRL) in Sf9 cells.

[0056] To determine their *in vitro* action on PDE9A, the test substances are dissolved in 100% DMSO and serially diluted. Typically, dilution series of 200 µM to 1.6 µM are prepared (resulting end concentration in the test: 4 µM to 0.032 µM). In each case, 2 µL of the diluted

substance solutions is placed in wells of microtiter plates (Isoplate; Wallac Inc., Atlanta, GA). Next, 50 μL of a dilution of the PDE9A preparation described above is added. The dilution of the PDE9A preparation is selected so that less than 70% of the substrate is converted during the later incubation (typical dilution: 1: 10,000; dilution buffer: 50 mM TRIS/HCl, pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA, 0.2% BSA). The substrate, [8-^{3}H] guanosine 3',5'-cyclic phosphate (1 μCi/μL; Amersham Pharmacia Biotech., Piscataway, NJ), is diluted 1:2000 with assay buffer (50 mM Tris/HCl, pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA) to a concentration of 0.0005 μCi/μL. The enzyme reaction is finally started by addition of 50 μL (0.025 μCi) of the diluted substrate. The test batches are incubated for 60 minutes at room temperature and the reaction is stopped by addition of 25 μL of a PDE9A inhibitor (e.g., the inhibitor from preparation example 1, 10 μM end concentration) dissolved in assay buffer. Directly thereafter, 25 μL of a suspension with 18 mg/mL of yttrium scintillation proximity beads (Amersham Pharmacia Biotech., Piscataway, NJ.) is added. The microtiter plates are sealed with film and allowed to stand for 60 minutes at room temperature. Next, the plates are measured for 30 seconds per well in a Microbeta scintillation counter (Wallac Inc., Atlanta, GA). IC_{50} values are determined from plots of the substance concentration vs. percentage of inhibition.

[0057] The *in vitro* action of test substances on recombinant PDE3B, PDE4B, PDE7B, PDE8A, PDE10A, and PDE11A is determined by the test protocol described above for PDE9A with following modifications: [5',8-^{3}H] adenosine 3',5'-cyclic phosphate (1 μCi/μL; Amersham Pharmacia Biotech., Piscataway, NJ) is used as the substrate. It is not necessary to add an inhibitor solution to stop the reaction. Instead, following the incubation of substrate and PDE, the addition of the yttrium scintillation proximity beads proceeds directly as described above and this stops the reaction. To determine a corresponding action on recombinant PDE1C, PDE2A, and PDE5A, the protocol is modified further as follows: for PDE1C, in addition calmodulin (10^{-7} M) and $CaCl_2$ (3 mM) are added to the reaction batch. PDE2A is stimulated in the test by addition of cGMP (1 μM) and tested with a BSA concentration of 0.01%. For PDE1C and PDE2A, [5',8-^{3}H] adenosine 3',5'-cyclic phosphate (1 μCi/μL; Amersham Pharmacia Biotech., Piscataway, NJ), and for PDE5A [8-^{3}H] guanosine 3',5'-cyclic phosphate (1 μCi/μL; Amersham Pharmacia Biotech., Piscataway, NJ) are used as the substrate.

[0058] The PDE9A-inhibiting action of the compounds of the invention can be demonstrated using the following examples in Tables 1 and 2:

Table 1: Inhibition of PDE Isozymes by Example 3

Isozymes	Species	IC_{50} [nM]
PDE1C	human	720
PDE2A	human	> 4000
PDE3B	human	> 4000
PDE4B	human	> 4000
PDE5A	human	> 4000
PDE7B	human	> 4000
PDE8A	human	> 4000
PDE9A	human	110
PDE10A	human	> 4000

Table 2: PDE9A-inhibiting Action of the Compounds of the Invention

Example	IC_{50} [nM]
1	5
3	110
4	30
6	6
12	65
17	86
19	390

Increasing the Intracellular Neuronal cGMP Concentration in Cell Cultures

[0059] PDE9A inhibitors increase the intracellular neuronal cGMP in cultured primary cortical neurons.

[0060] Rat embryos (embryonic day E17–E19) were decapitated; the heads were transferred to preparation dishes filled with preparation medium (DMEM, penicillin/streptomycin; both from Gibco). The scalp and skull cap were removed, and the exposed brains were transferred to another Petri dish with preparation medium. The cerebrum (cortex) was isolated using a binocular microscope and two forceps and cooled with ice to 4°C. This preparation and the separation of cortical neurons were then carried out according to a standard protocol using the papain kit (Worthington Biochemical Corporation, Lakewood, New Jersey 08701, USA) (Huettner *et al.*, *J. Neurosci.*, **1986**, *6*, 3044–3060). The mechanically isolated cortical neurons

were cultured with 150,000 cells/well in 200 µL of neurobasal medium/well (Neurobasal; B27 Supplement; 2 mM of L-glutamine; in the presence of penicillin/streptomycin; all agents from Gibco) for 7 days in 96 perforated plates (pretreated with poly-D-lysine, 100 µg/mL, for 30 minutes) under standard conditions (37°C, 5% CO_2). The medium was removed after 7 days and the cells washed with HBSS buffer (Hank's balanced salt solution, Gibco/BRL). Next, 100 µL of the compound of the invention dissolved in HBSS buffer (previously dissolved in 100% DMSO: 10 mM) is added to the cells. Next, 100 µL of HBSS buffer is again added, so that the end concentration of the compounds of the invention is, for example, in a range of 20 nM to 10 µM, and the cells are incubated at 37°C for 20 minutes. The test buffer is then completely removed. Next, the cells are lysed in 200 µL of lysis buffer (cGMP Kit code RPN 226; from Amersham Pharmacia Biotech.), and the cGMP concentration is measured according to the manufacturer's directions. All measurements are performed in triplicate. The statistical evaluation is performed using Prism Software version 2.0 (GraphPad Software Inc., San Diego, CA USA).

[0061] Incubation of the primary neurons with the compounds of the invention led to an increase in the cGMP content.

Long-term Potentiation

[0062] Long-term potentiation is regarded as a cellular correlate for learning and memory processes. The following procedure can be used to determine whether PDE9 inhibition has an effect on long-term potentiation:

Rat hippocampi are placed at an angle of about 70 degrees relative to the cutting blade (chopper). The hippocampus is cut at intervals of 400 µm. The sections are removed from the blade with using a very soft, very wet brush (marten hair) and transferred to a glass container with carbogenated cooled nutrient solution (124 mM NaCl, 4.9 mM KCl, 1.3 mM $MgSO_4 * 7H_2O$, 2.5 mM $CaCl^{2+}$ anhydrous, 1.2 mM KH_2PO_4, 25.6 mM $NaHCO_3$, 10 mM glucose, pH 7.4). During the measurement, the sections are located in a temperature-controlled chamber under a liquid level 1–3 mm in height. The flow-through rate is 2.5 mL/min. The pregassing occurs at low excess pressure (about 1 atm) and through a microcannula in the prechamber. The slice chamber is connected to the prechamber in such a manner that a minicirculation can be maintained. Carbogen flowing out of the microcannula is used as the drive for the minicirculation. The freshly prepared hippocampus slices are adapted in the slice chamber for at least 1 hour at 33°C.

[0063] The stimulus intensity is selected so that the focal excitatory postsynaptic potentials (fEPSP) constitute 30% of the maximum excitatory postsynaptic potential (EPSP). The Schaffer

collaterals are stimulated locally using a monopolar stimulation electrode, which consists of enameled stainless steel and a constant current, biphasic stimulus generator (AM-Systems 2100) (voltage: 1 to 5 V, pulse duration with a polarity of 0.1 ms, total pulse 0.2 ms). The excitatory postsynaptic potentials (fEPSP) from the stratum radiatum are recorded using glass electrodes (borosilicate glass with filament, 1 to 5 MOhm, diameter: 1.5 mm, major diameter of thread: 3 to 20 μm), which are filled with normal nutrient solution. The field potentials are measured using a direct-current amplifier versus a chlorinated silver reference electrode, which is located at the edge of the slice chamber. The field potentials are filtered through a low-pass filter (5 kHz). The slope of the fEPSPs (fEPSP slope) is determined for the statistical analysis of the experiment. The recording, analysis, and control of the experiment are carried out using a software program (PWIN), which was developed in the Department of Neurophysiology. EXCEL software was used to determine the means for the fEPSP slope values at the specific times and to plot the diagrams; here, an appropriate macro automates the recording of the data.

[0064] Superfusion of the hippocampal sections with a 10-μM solution of the compounds of the invention leads to a significant increase in the long-term potentiation.

Social Recognition Test:

[0065] The social recognition test is a learning and memory test. It measures the ability of rats to differentiate between known and unknown individuals of the same species. For this reason, this test is suitable for studying the learning- or memory-improving action of the compounds of the invention.

[0066] Adult rats, kept in groups, are placed individually in test cages 30 minutes before the start of the test. Four minutes before the start of the test, the test animal is placed in an observation box. After this adaptation time, a juvenile animal is placed with the test animal and the absolute time for which the adult animal inspects the young one is measured for 2 minutes (trial 1). All behavior clearly directed at the young animal, during which the older animal is located at a distance of at most 1 cm from the young animal, is measured, i.e., anogenital inspection, pursuit, and fur grooming. The juvenile is then removed; the adult is treated with one of the compounds of the invention or vehicle and then returned to its home cage. After a retention time of 24 hours, the test is repeated (trial 2). A reduced social interaction time compared with trial 1 indicates that the adult rat remembers the young animal.

[0067] The adult animals are injected intraperitoneally immediately after trial 1 either with vehicle (10% ethanol, 20% Solutol, and 70% physiological saline solution) or 0.1 mg/kg, 0.3

mg/kg, 1.0 mg/kg, or 3.0 mg/kg of the compound of the invention, dissolved in 10% ethanol, 20% Solutol, or 70% physiological saline solution. Vehicle-treated rats show no reduction in the social interaction time in trial 2 compared with trial 1. They have subsequently forgotten that they already had contact with the young animal. Surprisingly, the social interaction time in the second run after treatment with the compounds of the invention is significantly reduced compared with the vehicle. This means that the substance-treated rats remembered the juvenile animal and thus the compounds of the invention have a memory- and learning-improving action.

[0068] The new active substances can be converted into customary formulations in a known manner, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions, and solutions, using inert, nontoxic, pharmaceutically suitable carrier substances or solvents. In this case, the therapeutically effective compound should be present in each case in a concentration of about 0.5 to 90% by weight of the total mixture, i.e., in amounts sufficient to achieve the indicated dosage range.

[0069] The formulations are prepared, for example, by extending the active substance with solvents and/or carrier substances, optionally with use of emulsifiers and/or dispersants, whereby, e.g., if water is used as the diluent, if applicable, organic solvents can be used as solubilizers.

[0070] The administration occurs in a customary manner, preferably orally, transdermally, or parenterally, especially perlingually or intravenously. It can also occur, however, by means of inhalation through the mouth or nose, for example, using a spray, or topically via the skin.

[0071] In general, it has proven advantageous to administer amounts of about 0.001 to 10, with oral use preferably about 0.005 to 3 mg/kg of body weight to achieve an effective result.

[0072] Nonetheless, it can be necessary, where appropriate, to deviate from the indicated amounts, to wit, depending on body weight or the route of administration, individual response to the medicament, the type of formulation thereof, and the time or interval at which the administration occurs. Thus, it can be sufficient in some cases to manage with less than the aforementioned minimum amount, whereas in other cases the indicated top limit must be exceeded. If rather high amounts are administered, it may be advisable to distribute said amount in several individual doses over the day.

[0073] If not otherwise indicated, all quantity data refer to percentages by weight. Solvent ratios, dilution ratios, and concentration data for liquid/liquid solutions refer in each case to the volume. The statement "w/v" stands for "weight/volume." Thus, for example, "10% w/v" means that 100 mL of solution or suspension contains 10 g of substance.

Employed abbreviations:

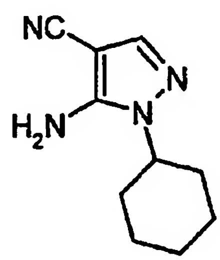
[0074] BSA bovine serum albumin

DCI	direct chemical ionization (in MS)
DMSO	dimethylsulfoxide
of th.	of theoretical (in reference to yield)
EDTA	ethylene diamine tetraacetic acid
equiv.	equivalents
ESI	electrospray ionization (in MS)
HATU	O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
Lit.	literature reference
MS	mass spectroscopy
NMR	nuclear magnetic resonance (spectroscopy)
mp	melting point
Tris	Tris(hydroxymethyl)aminomethane

Starting Compounds:

Example 1A

5-Amino-1-cyclohexyl-1H-pyrazole-4-carbonitrile



[0075] A solution of cyclohexylhydrazine hydrochloride (3 g, 19.9 mmol) in 36 mL of ethanol is combined at room temperature first with ethoxymethylene malonic acid dinitrile (2.43 g, 19.9 mmol) and then with 8 mL of triethylamine. The mixture is refluxed for 20 minutes and then cooled. The solvent is stripped off with a rotary evaporator, and the residue taken up in DCM, washed with aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered, and concentrated by evaporation in vacuum. The crude product is chromatographed on silica gel (solvent: dichloromethane/methanol 0-10%).

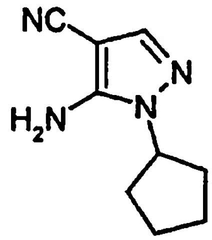
[0076] Yield: 1.95 g (51% of th.)

MS (DCI): m/z = 191 $(M + H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 7.5 (s, 1H), 6.5 (s, 2H), 4.0 (m, 1H), 1.95-1.05 (m, 10H) ppm.

Example 2A

5-Amino-1-cyclopentyl-1H-pyrazole-4-carbonitrile



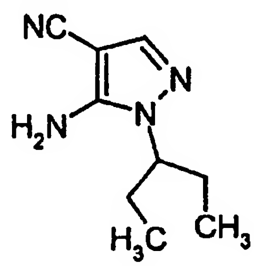
[0077] The preparation proceeds as described in the directions for Example 1A.

[0078] MS (ESI): m/z = 177 $(M + H)^+$

^{1}H-NMR (200 MHz, $CDCl_3$): δ =7.5 (s, 1H), 4.45 (br. s, 2H), 4.35 (m, 1H), 2.2-1.55 (m, 6H) ppm.

Example 3A

5-Amino-1-(1-ethylpropyl)-1H-pyrazole-4-carbonitrile



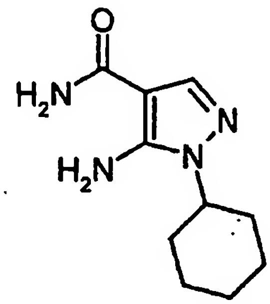
[0079] The preparation proceeds as described in the directions for Example 1A.

[0080] MS (ESI): m/z = 179 $(M + H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ =7.55 (s, 1H), 6.45 (s, 2H), 4.0 (m, 1H), 1.8-1.55 (m, 4H), 0.65 (t, 6H) ppm.

Example 4A

5-Amino-1-cyclohexyl-1H-pyrazole-4-carboxamide



[0081] A solution of 5-amino-1-cyclohexyl-1H-pyrazole-4-carbonitrile (1.86 g, 9.81 mmol) in a mixture of 73 mL of ethanol and 90 mL of concentrated aqueous ammonia solution is combined at room temperature with 18 mL of a 30% hydrogen peroxide solution and stirred for 1 hour at room temperature. Next, the nonaqueous solvents are stripped off in the rotary evaporator. The product precipitates from the remaining mixture as a solid, which is filtered with suction, washed with a small amount of water, and dried in high vacuum.

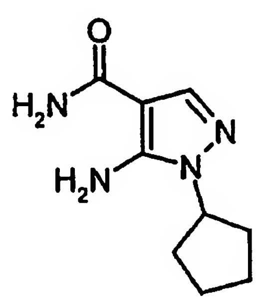
[0082] Yield: 1.77 g (86% of th.)

MS (DCI): m/z = 209 $(M + H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ =7.6 (s, 1H), 7.3-6.4 (broad, 2H), 6.1 (s, 2H), 3.95 (m, 1H), 1.95-1.05 (m, 10H) ppm.

Example 5A

5-Amino-1-cyclopentyl-1H-pyrazole-4-carboxamide



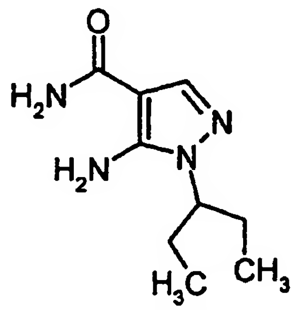
[0083] The preparation proceeds as described in the directions for Example 4A.

[0084] MS (ESI): m/z = 195 $(M + H)^+$

^{1}H-NMR (200 MHz, $CDCl_3$): δ =7.5 (s, 1H), 5.6-4.8 (wide, 4H), 4.35 (m, 1H), 2.2-1.55 (m, 8H) ppm.

Example 6A

5-Amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide



[0085] The preparation proceeds as described in the directions for Example 4A.

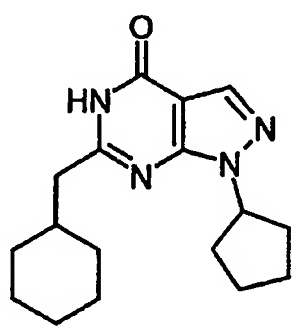
[0086] MS (ESI): m/z = 197 $(M + H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ =7.65 (s, 1H), 6.9 (br. s, 2H), 6.1 (s, 2H), 3.9 (m, 1H), 1.85-1.6 (m, 4H), 0.7 (t, 6H) ppm.

Exemplary Embodiments:

Example 1

6-(Cyclohexylmethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidin-4-one



[0087] 75 mg (0.39 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 183 mg (1.16 mmol, 3 equiv.) of cyclohexylacetic acid methyl ester in 1.5 mL of absolute ethanol are charged under argon. 54 mg of sodium hydride (60% dispersion in mineral oil; 1.35 mmol, 3.5 equiv.) is slowly added at 0°C in an argon countercurrent flow. The resulting mixture is slowly heated and stirred for 18 hours under reflux. For the workup, 20 mL of water is added and the mixture is extracted repeatedly with ethyl acetate. The pooled organic phases are dried over sodium sulfate and concentrated by evaporation in vacuum. The crude product is purified by means of preparative HPLC.

[0088] Yield: 36 mg (31% of th.)

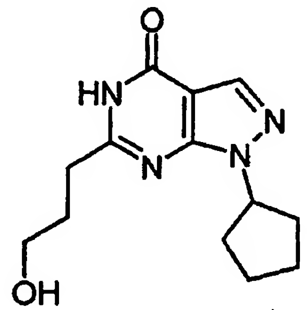
MS (ESI): m/z = 301 $(M + H)^+$

mp: 147°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ =11.95 (s, 1H), 8.0 (s, 1H), 5.1 (m, 1H), 2.5 (d, 2H), 2.15-1.75 (m, 7H), 1.75-1.55 (m, 7H), 1.3-0.9 (m, 5H) ppm.

Example 2

1-Cyclopentyl-6-(3-hydroxypropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0089] As described in Example 1, the product is obtained starting from 75 mg (0.39 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 140 mg (1.16 mmol) of 4-hydroxybutyric acid methyl ester.

[0090] Yield: 85 mg (84% of th.)

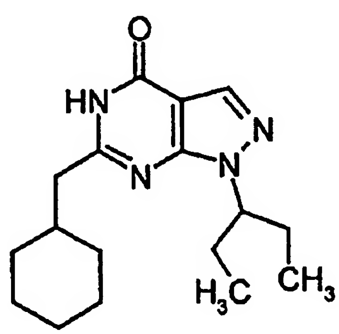
MS (DCI): m/z = 263 $(M + H)^+$

mp: 138°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =8.0 (s, 1H), 5.1 (m, 1H), 3.5 (t, 2H, J = 6.5 Hz), 2.65 (t, 2H, J = 7.5 Hz), 2.2-1.55 (m, 10H) ppm.

Example 3

6-(Cyclohexylmethyl)-1-(1-ethylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0091] As described in Example 1, the product is obtained starting from 200 mg (1.02 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 482 mg (3.06 mmol) of cyclohexylacetic acid methyl ester.

[0092] Yield: 146 mg (47% of th.)

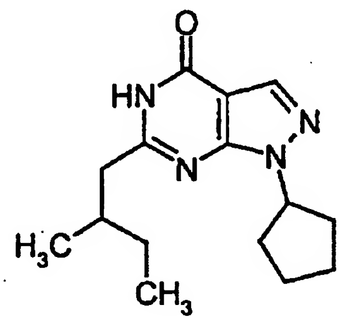
MS (ESI): m/z = 303 $(M + H)^+$

mp: 122°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.0 (s, 1H), 8.0 (s, 1H), 4.45 (m, 1H), 2.5 (m, 2H), 2.0-1.5 (m, 10H), 1.4-0.9 (m, 5H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 4

1-Cyclopentyl-6-(2-methylbutyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0093] As described in Example 1, the product is obtained starting from 200 mg (1.01 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 450 mg (3.03 mmol) of 3-methylvaleric acid ethyl ester.

[0094] Yield: 88 mg (32% of th.)

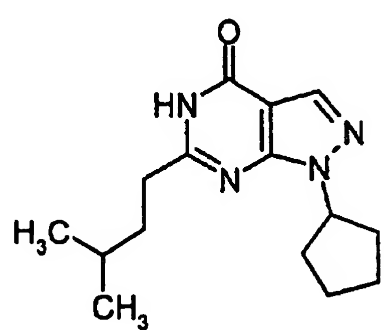
MS (DCI): m/z = 275 $(M + H)^+$

mp: 86°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.0 (s, 1H), 8.0 (s, 1H), 5.1 (m, 1H), 2.65 (dd, 1H), 2.45 (dd, 1H), 2.15-1.8 (m, 7H), 1.7 (m, 2H), 1.45-1.15 (m, 2H), 0.9 (m, 6H) ppm.

Example 5

1-Cyclopentyl-6-(3-methylbutyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0095] As described in Example 1, the product is obtained starting from 200 mg (1.01 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 450 mg (3.03 mmol) of 4-methylvaleric acid ethyl ester.

[0096] Yield: 165 mg (60% of th.)

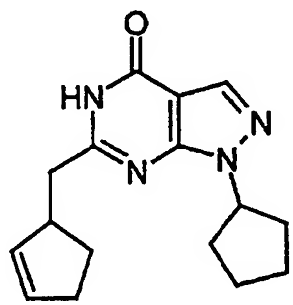
MS (ESI): m/z = 275 $(M + H)^+$

mp: 133°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.0 (s, 1H), 8.0 (s, 1H), 5.1 (m, 1H), 2.6 (m, 2H), 2.2-1.5 (m, 11H), 0.9 (d, 6H, J = 6.5 Hz) ppm.

Example 6

6-(2-Cyclopenten-1-ylmethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidin-4-one



[0097] As described in Example 1, the product is obtained starting from 200 mg (1.01 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 446 mg (1.82 mmol, 95% pure) of 2-cyclopenten-1-ylacetic acid methyl ester (Lit.: Roenn *et al.*, *Tetrahedron Lett.* **1995**, *36*, 7749).

[0098] Yield: 86 mg (30% of th.)

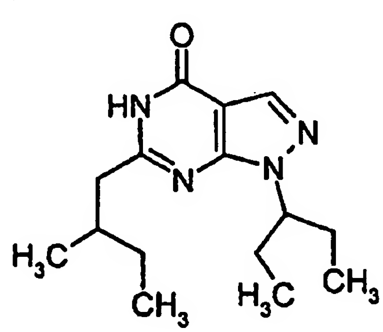
MS (ESI): m/z = 285 $(M + H)^+$

mp: 166°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.0 (s, 1H), 8.0 (s, 1H), 5.75 (m, 2H), 5.1 (m, 1H), 3.15 (m, 1H), 2.8-2.5 (m, 2H), 2.45-1.45 (m, 12H) ppm.

Example 7

1-(1-Ethylpropyl)-6-(2-methylbutyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0099] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 445 mg (3.0 mmol) of 3-methylvaleric acid ethyl ester.

[0100] Yield: 99 mg (36% of th.)

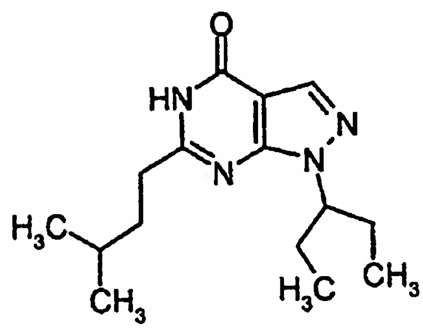
MS (ESI): m/z = 277 $(M + H)^+$

mp: 121°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.0 (s, 1H), 8.0 (s, 1H), 4.5 (m, 1H), 2.6 (dd, 1H), 2.45 (dd, 1H), 2.05-1.7 (m, 5H), 1.45-1.15 (m, 2H), 0.9 (m, 6H), 0.65 (t, 6H, J = 7.5 Hz) ppm.

Example 8

1-(1-Ethylpropyl)-6-isopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0101] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 445 mg (3.0 mmol) of 4-methylvaleric acid ethyl ester.

[0102] Yield: 127 mg (46% of th.)

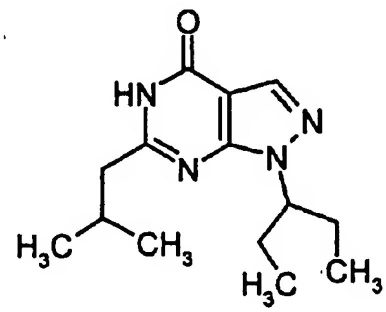
MS (ESI): m/z = 277 $(M + H)^+$

mp: 127°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.0 (s, 1H), 8.0 (s, 1H), 4.45 (m, 1H), 2.65 (m, 2H), 2.0-1.8 (m, 4H), 1.7-1.5 (m, 3H), 0.9 (d, 6H, J = 7 Hz), 0.6 (t, 6H, J = 6 Hz) ppm.

Example 9

1-(1-Ethylpropyl)-6-isobutyl-1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidin-4-one



[0103] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 464 mg (3.5 mmol) of 3-methylbutyric acid ethyl ester.

[0104] Yield: 127 mg (48% of th.)

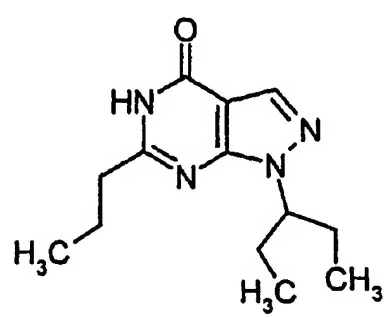
MS (ESI): m/z = 263 $(M + H)^+$

mp: 161°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.0 (s, 1H), 8.0 (s, 1H), 4.45 (m, 1H), 2.5 (m, 2H), 2.15 (m, 1H), 1.95-1.75 (m, 4H), 0.9 (d, 6H, J = 7 Hz), 0.55 (t, 6H, J = 7.5 Hz) ppm.

Example 10

1-(1-Ethylpropyl)-6-propyl-1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidin-4-one



[0105] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 410 mg (3.5 mmol) of butyric acid ethyl ester.

[0106] Yield: 159 mg (64% of th.)

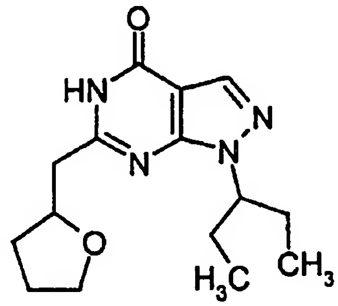
MS (ESI): m/z = 249 $(M + H)^+$

mp: 127°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.95 (s, 1H), 8.0 (s, 1H), 4.5 (m, 1H), 2.6 (t, 2H, J = 7.5 Hz), 2.0-1.65 (m, 6H), 0.9 (t, 3H, J = 7.5 Hz), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 11

1-(1-Ethylpropyl)-6-(tetrahydro-2-furanylmethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one



[0107] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 553 mg (3.5 mmol) of tetrahydrofuran-2-ylacetic acid ethyl ester.

[0108] Yield: 202 mg (68% of th.)

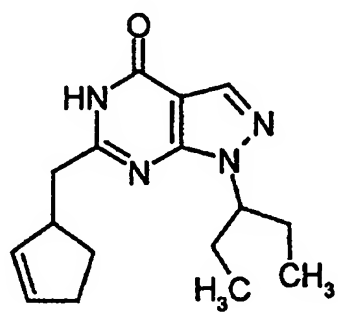
MS (ESI): m/z = 291 $(M + H)^+$

mp: 136°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.0 (s, 1H), 8.0 (s, 1H), 4.45 (m, 1H), 4.25 (m, 1H), 3.75 (m, 1H), 3.6 (m, 1H), 2.8 (m, 2H), 2.1-1.55 (m, 8H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 12

6-(2-Cyclopenten-1-ylmethyl)-1-(1-ethylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one



[0109] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 490 mg (3.5 mmol) of 2-cyclopenten-1-ylacetic acid methyl ester (Lit.: Roenn *et al.*, *Tetrahedron Lett.* **1995**, *36*, 7749).

[0110] Yield: 111 mg (39% of th.)

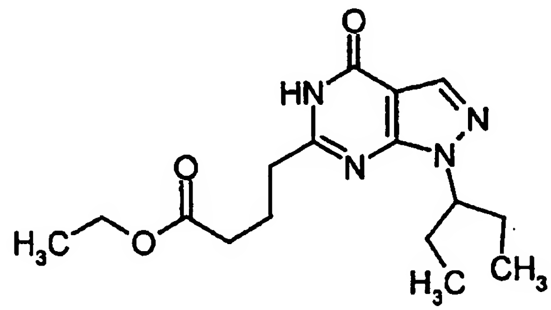
MS (ESI): m/z = 287 $(M + H)^+$

mp: 128°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.0 (s, 1H), 8.0 (s, 1H), 5.8-5.65 (m, 2H), 4.5 (m, 1H), 3.2 (m, 1H), 2.8-2.55 (m, 2H), 2.3 (m, 2H), 2.15-1.8 (m, 5H), 1.55 (m, 1H), 0.65 (t, 6H, J = 7.5 Hz) ppm.

Example 13

4-[1-(1-Ethylpropyl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]butyric acid ethyl ester



[0111] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 1.13 mg (6.0 mmol) of glutaric acid diethyl ester.

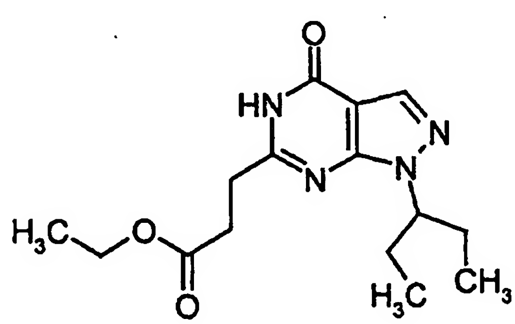
[0112] Yield: 46 mg (13% of th.)

MS (ESI): m/z = 321 (M + H)+

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.0 (s, 1H), 8.0 (s, 1H), 4.5 (m, 1H), 4.2 (q, 2H, J = 7 Hz), 2.7 (t, 2H, J = 7.5 Hz), 2.4 (t, 2H, J = 7 Hz), 2.1-1.75 (m, 6H), 1.2 (t, 3H, J = 7 Hz), 0.65 (t, 6H, J = 7.5 Hz) ppm.

Example 14

4-[1-(1-Ethylpropyl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]propionic acid ethyl ester



[0113] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 1.04 g (6 mmol) of succinic acid diethyl ester.

[0114] Yield: 176 mg (56% of th.)

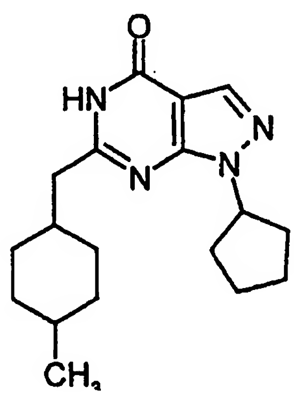
MS (ESI): m/z = 307 $(M + H)^+$

mp: 118°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.1 (s, 1H), 8.0 (s, 1H), 4.4 (m, 1H), 4.0 (q, 2H, J = 7 Hz), 2.9 (m, 2H), 2.8 (m, 2H), 2.0-1.7 (m, 4H), 1.2 (t, 3H, J = 7 Hz), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 15

1-Cyclopentyl-6-[(4-methylcyclohexyl)methyl]-1,5-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one



[0115] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 664 mg (3.5 mmol) of (4-methylcyclohexyl)acetic acid ethyl ester (cis/trans mixture). The product is present as a mixture of the cis and trans isomers.

[0116] Yield: 131 mg (41% of th.)

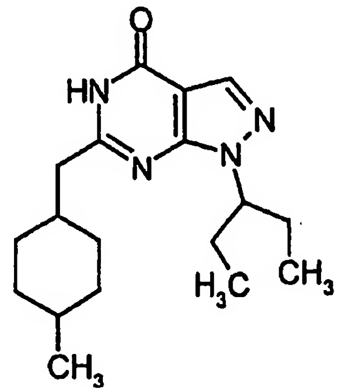
MS (ESI): m/z = 315 $(M + H)^+$

mp: 126°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.0 (s, 1H), 8.0 (s, 1H), 5.1 (m, 1H), 2.6 (d, 2H, J = 7 Hz), 2.2-0.8 (m, 21H) ppm.

Example 16

1-(1-Ethylpropyl)-6-[(4-methylcyclohexyl)methyl]-1,5-dihydro-4H-pyrazolo[3,4-d]-pyrimidin-4-one



[0117] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 413 mg (2.2 mmol) of (4-methylcyclohexyl)acetic acid ethyl ester (cis/trans mixture). The product is present as a mixture of the cis and trans isomers.

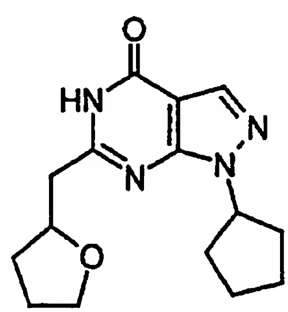
[0118] Yield: 60 mg (19% of th.)

MS (ESI): m/z = 317 $(M + H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.0 (s, 1H), 8.0 (s, 1H), 4.45 (m, 1H), 2.6 (d, 2H, J = 7 Hz), 2.2-0.8 (m, 17H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 17

1-Cyclopentyl-6-(tetrahydro-2-furanylmethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0119] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 559 mg (3.5 mmol) of tetrahydro-furan-2-ylacetic acid ethyl ester.

[0120] Yield: 175 mg (60% of th.)

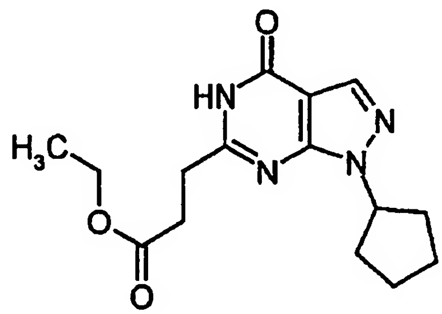
MS (ESI): m/z = 289 $(M + H)^+$

mp: 179°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =11.95 (s, 1H), 8.0 (s, 1H), 5.1 (m, 1H), 4.3 (m, 1H), 3.8 (m, 1H), 3.6 (m, 1H), 2. 8 (m, 2H), 2.15-1.5 5 (m, 12H) ppm.

Example 18

4-[1-Cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]propionic acid ethyl ester



[0121] As described in Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 1.05 g (6.05 mmol) of succinic acid diethyl ester.

[0122] Yield: 150 mg (49% of th.)

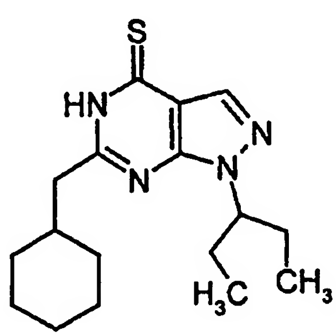
MS (DCI): m/z = 305 $(M + H)^+$

mp: 185°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.1 (s, 1H), 8.0 (s, 1H), 5.05 (m, 1H), 4.05 (q, 2H, J = 7 Hz), 2.9 (m, 2H), 2.8 (m, 2H), 2.15-1.6 (m, 8H), 1.2 (t, 3H, J = 7 Hz) ppm.

Example 19

6-(Cyclohexylmethyl)-1-(1-ethylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-thione



[0123] A solution of 50 mg (0.17 mmol) of 6-(cyclohexylmethyl)-1-(1-ethylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Example 3) in 1 mL of pyridine is combined at room

temperature with 74 mg (0.33 mmol, 2 equiv.) of diphosphorus pentasulfide and then stirred overnight under reflux. After cooling, the reaction solution is combined with 20 mL of ice-cold 2.5% sodium bicarbonate solution and extracted three times with ethyl acetate. The pooled organic phases are washed with saturated saline solution, dried over sodium sulfate, and concentrated by evaporation in vacuum. The crude product is purified by preparative HPLC.

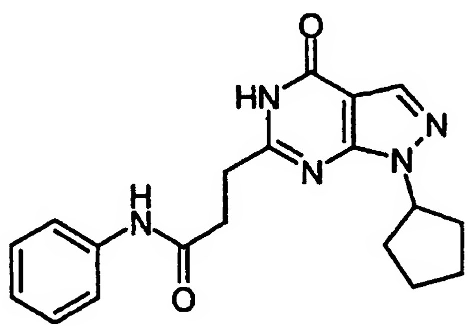
[0124] Yield: 42 mg (80% of th.)

MS (DCI): m/z = 319 $(M + H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ =13.4 (s, 1H), 8.2 (s, 1H), 4.45 (m, 1H), 2.7 (d, 2H, J = 7 Hz), 2.0-1.5 (m, 10H), 1.4-0.85 (m, 5H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 20

3-(1-Cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-*N*-phenylpropanamide



[0125] A solution of 100 mg (0.33 mmol) of 4-[1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]propionic acid ethyl ester (Example 18) in a mixture of 1 mL of ethanol and 0.5 mL of 20% sodium hydroxide solution is stirred for 1 hour at 60°C. The organic solvent fraction is stripped off in a rotary evaporator and the solution is adjusted to pH 3 with 1*N* hydrochloric acid. The solution is then evaporated to dryness, the residue is stirred with 5 mL of methanol, and the solution is filtered. After the methanol is stripped off, the corresponding carboxylic acid is obtained as the crude product (90 mg, quantitative).

[0126] 87 mg (0.31 mmol) of the thus obtained carboxylic acid is introduced into 6 mL of dichloromethane and combined first with 119 mg (0.31 mmol, 1 equiv.) of HATU and then with 29 mg (0.31 mmol, 1 equiv.) of aniline and 81 mg (0.63 mmol, 2 equiv.) of *N*-ethyldiisopropylamine and stirred overnight. For the workup, the reaction solution is washed twice with saturated sodium bicarbonate solution; the organic phase is dried over sodium sulfate and concentrated by evaporation in vacuum. The crude product is purified by means of preparative HPLC.

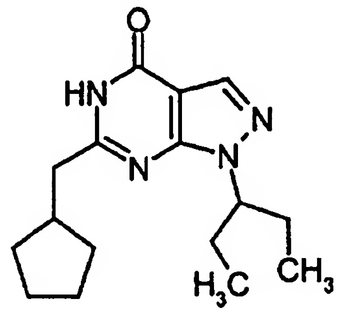
[0127] Yield: 25 mg (22% of th.)

MS (ESI): m/z = 352 $(M + H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ =12.05 (s, 1H), 10.1 (s, 1H), 8.0 (s, 1H), 7.6 (d, 2H), 7.3 (t, 2H), 7.0 (t, 1H), 5.0 (m, 1H), 3.0 (m, 2H), 2.8 (m, 2H), 2.05-1.4 (m, 8H) ppm.

Example 21

6-(Cyclopentylmethyl)-1-(1-ethylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



[0128] As described in Example 1, the product is obtained starting from 150 mg (0.75 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 351 mg (2.25 mmol) of 2-cyclopentylacetic acid ethyl ester.

[0129] Yield: 91 mg (42% of th.)

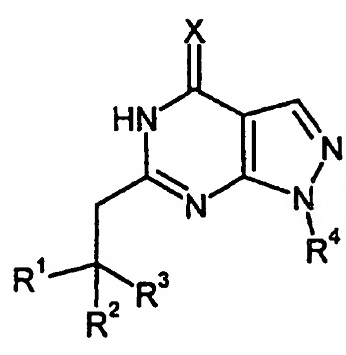
MS (ESI): m/z = 289 $(M + H)^+$

mp: 156°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.0 (s, 1H), 8.0 (s, 1H), 4.45 (m, 1H), 2.7 (d, 2H, J = 7.5 Hz), 2.3 (m, 1H), 2.0-1.45 (m, 10H), 1.35-1.1 (m, 2H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Claims

1. Compounds of the formula



(I),

where

R^1 stands for C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, -C(=O)OR^5, or -C(=O)NR^{6}R^7, whereby C_1-C_6 alkyl is optionally substituted with hydroxy, C_1-C_6 alkoxy, -C(=O)OR^5, or -C(=O)NR^{6}R^7, and
R^5 for C_1-C_6 alkyl,
R^6 and R^7 independently of one another for hydrogen, C_6-C_{10} aryl, C_1-C_6 alkyl, or,
together with the nitrogen atom to which they are bound, form a 4- to 10-membered heterocyclyl,
R^2 stands for hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy,
or
R^1 and R^2, together with the carbon atom to which they are bound, form C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, or a 4- to 10-membered heterocyclyl, which are optionally substituted with up to 2 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, oxo, and -C(=O)OR^8, and
R^8 stands for C_1-C_6 alkyl or benzyl,
R^3 represents hydrogen or C_1-C_6 alkyl,
R^4 pentan-3-yl or C_4-C_6 cycloalkyl,
X oxygen or sulfur,
and salts thereof, solvates, and/or solvates of the salts.

2. Compounds according to claim 1, where
R^1 stands for C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, -C(=O)OR^5, or -C(=O)NR^{6}R^7, whereby C_1-C_4 alkyl is optionally substituted with hydroxy, C_1-C^4 alkoxy, -C(=O)OR^5, or -C(=O)NR^{6}R^7, and
R^5 stands for C_1-C_4 alkyl,
R^6 and R^7 independently of one another for hydrogen, phenyl, and C_1-C_4 alkyl, or, together with the nitrogen atom to which they are bound, form a 5- to 6-membered heterocyclyl,
R^2 stands for hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy,
or
R^1 and R^2, together with the carbon atom to which they are bound, form C_5-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, or a 5- to 6-membered heterocyclyl, which are optionally substituted with up to 2 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, oxo, and -C(=O)OR^8, and
R^8 stands for C_1-C_4 alkyl or benzyl,
R^3 represents hydrogen,
R^4 pentan-3-yl or C_5-C_6 cycloalkyl,

X oxygen or sulfur,

and salts thereof, solvates, and/or solvates of the salts.

3. Compounds according to claims 1 and 2, wherein

R^1 stands for methyl, ethyl, isopropyl, methoxycarbonyl, ethoxycarbonyl, or -C(=O)NR^6R^7, whereby methyl is optionally substituted with methoxycarbonyl or ethoxycarbonyl, and

R^6 stands for phenyl, and

R^7 stands for hydrogen,

R^2 represents hydrogen, methyl, or

R^1 and R^2, together with the carbon atoms to which they are bound, form cyclopentyl, cyclohexyl, cyclopentenyl, or tetrahydrofuryl, whereby cyclohexyl is optionally substituted with methyl, and

R^3 represents hydrogen,

R^4 pentan-3-yl or C_5-C_6 cycloalkyl,

X oxygen or sulfur,

and salts thereof, solvates, and/or solvates of the salts.

4. Compounds according to claims 1 through 3, wherein

R^1 stands for methyl, ethyl, isopropyl, methoxycarbonyl, ethoxycarbonyl, or -C(=O)NR^6R^7, whereby methyl is optionally substituted with methoxycarbonyl or ethoxycarbonyl, and

R^6 for phenyl, and

R^7 for hydrogen,

R^2 represents hydrogen, methyl, or

R^1 and R^2, together with the carbon atoms to which they are bound, form cyclopentyl, cyclohexyl, cyclopentenyl, or tetrahydrofuryl, whereby cyclohexyl is optionally substituted with methyl, and

R^3 represents hydrogen,

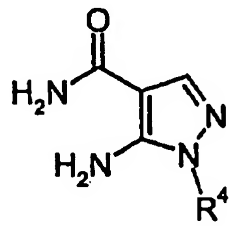
R^4 pentan-3-yl or C_5-C_6 cycloalkyl,

X oxygen,

and salts thereof, solvates, and/or solvates of the salts.

5. Method for the preparation of compounds according to claims 1 through 4, characterized in that

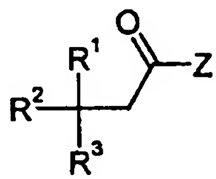
[A] compounds of the formula



(II),

where R^4 has the aforementioned meanings,

are converted by reaction with a compound of the formula



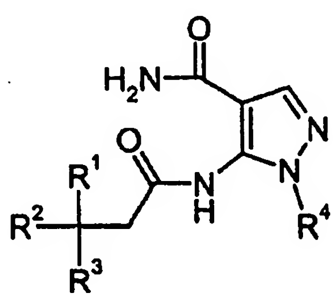
(IIIa),

where R^1, R^2 and R^3 have the aforementioned meanings,

and

Z stands for chlorine or bromine,

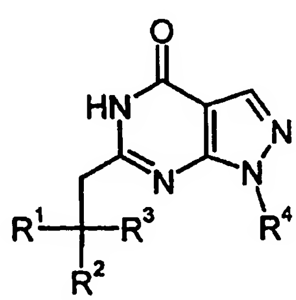
in an inert solvent and in the presence of a base, first into compounds of formula



(IV),

where R^1, R^2, R^3 and R^4 have the aforementioned meanings,

then cyclized in an inert solvent in the presence of a base to compounds of the formula

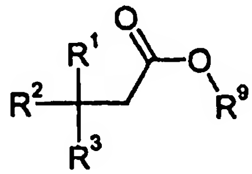


(IA),

where R^1, R^2, R^3, and R^4 have the aforementioned meanings,

or

[B] compounds of formula (II) are reacted with direct cyclization to (IA) with a compound of the formula



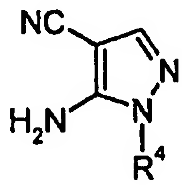
(IIIb),

where R^1, R^2, and R^3 have the aforementioned meanings, and

R^9 stands for methyl or ethyl,

in an inert solvent and in the presence of a base, or

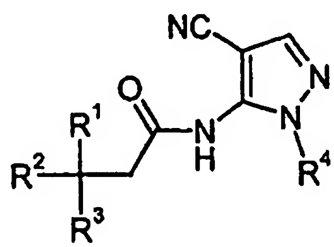
[C] compounds of the formula



(V),

where R^4 has the aforementioned meanings,

are converted first by reaction with a compound of formula (IIIa) in an inert solvent and in the presence of a base, into compounds of the formula

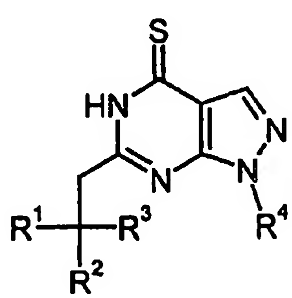


(VI),

where R^1, R^2, R^3, and R^4 have the aforementioned meanings,

and these are cyclized to (IA) in a second step in an inert solvent and in the presence of a base and an oxidizing agent,

and the compounds of formula (IA) are then converted optionally by reaction with a sulfurizing agent, such as, for example, diphosphorus pentasulfide, into the thiono derivatives of the formula



(IB),

where R^1, R^2, R^3, and R^4 have the aforementioned meanings,

and the resulting compounds of formula (I) are optionally reacted with the appropriate (i) solvents and/or (ii) bases or acids to their solvates, salts, and/or solvates of the salts.

6. Compounds according to any one of claims 1 through 4 for the treatment and/or prophylaxis of diseases.

7. Drugs containing at least one of the compounds according to any one of claims 1 through 4 and at least one pharmaceutically compatible, substantially nontoxic carrier or excipient.

8. Use of the compounds according to any one of claims 1 through 4 for the preparation of a medicament for the prophylaxis and/or treatment of disorders of cognition, concentration, learning capacity, and/or memory performance.

9. Use according to claim 8, wherein the disorder is a result of Alzheimer's disease.

10. Use of the compounds according to any one of claims 1 through 4 for the preparation of a medicament for the improvement of cognition, concentration, learning capacity, and/or memory performance.

11. Method for the control of disorders of cognition, concentration, learning capacity, and/or memory performance in humans or animals, through the administration of an effective amount of the compounds from claims 1 through 4.

12. Method according to claim 11 wherein the disorder is a result of Alzheimer's diseases.

No pages of drawings follow.